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Forschner-Dancausse, S., LaPlante, K., Smith, D. C., & Rowley, D. C. (2012). Going Deep for Drug Discovery: An Ocean to Bedside Approach to Explore Sub-Seafloor Microbes for the Next Generation of Antibiotics. *Medicine and Health, Rhode Island, 95*(9), 292-293. Retrieved from http://www.rimed.org/medhealthri/2012-09/2012-09-292.pdf
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Going Deep for Drug Discovery: An Ocean to Bedside Approach to Explore Sub-Seafloor Microbes for the Next Generation of Antibiotics

Stephanie Forschner-Dancause, PhD, Kerry LaPlante, PharmD, David C. Smith, PhD, and David C. Rowley, PhD

The World Health Organization has identified antimicrobial resistance as one of the top three greatest threats to human health. Today, infections by **methicillin-resistant *Staphylococcus aureus* (MRSA)** account for more deaths in US hospitals than both tuberculosis and HIV/AIDS combined.[1] More than 60% of staph infections in intensive care units are due to drug resistant strains,[1] and it is common to encounter those that lack sensitivity to multiple classes of drugs.[2] In addition, pathogenic *Escherichia coli* and *Klebsiella pneumoniae* are increasingly found to produce an extended spectrum of enzymes that significantly decrease drug options for treating infections and often leave patients with limited to no antimicrobial treatment options. Regrettably, antimicrobial research and development is not keeping pace with rising drug resistance.[3] There are currently no novel drugs in late stage development for the treatment of multidrug-resistant Gram-negative pathogens.

This leads scientists and clinicians to ask, "*Where will the next generation of antibiotics come from*?" A crucial component in drug discovery methods should continue to be the proven strategy of screening molecules from nature. Most of our clinically important antibiotics such as penicillins, tetracyclines, and macrolides have been discovered through the study of secondary metabolites produced by terrestrial microorganisms. In recent years, however, the repeated cultivation of the same microbial species from terrestrial soils has resulted in disappointing outcomes.[4] Frontier resources for the discovery of novel molecules are therefore critical to meet the genuine need for new antibiotics.

Exploring the Ocean

More than 70% of the earth's surface is comprised of ocean, and about 60% of the ocean floor is covered by water more than 2000 meters deep. Due to obvious technical challenges, sediments underlying the deep ocean remain one of the least explored environments for microbiology. At all taxonomic levels, there is more diversity of life in the deep sea than initially imagined.[5] Such biodiversity leads one to believe that the deep sea represents the next frontier in the search for exploitable biology.[6]

Collaboration

A new collaboration was formed by URI scientists to capitalize on the potential to discover new antibiotics produced by microbes from deep oceanic sediments. This interdisciplinary collaboration taps existing strengths in the fields of deep ocean microbiology (Smith lab, Graduate School of Oceanography), marine-based antibiotic drug discovery (Rowley Lab, College of Pharmacy), and evaluation (LaPlante Lab, VA Medical Center). It further leverages the opportunity to access deep oceanic sediments collected during expeditions conducted by the **Integrated Ocean Drilling Program (IODP)**. This scientific ocean drilling program, supported by 25 countries, and its predecessors the **Deep Sea Drilling Project (DSDP)** and the **Ocean Drilling Program (ODP)**, has retrieved sediment core samples from around the globe since 1968. Exploration of the subseafloor microbial community began in earnest in the late 1990s.

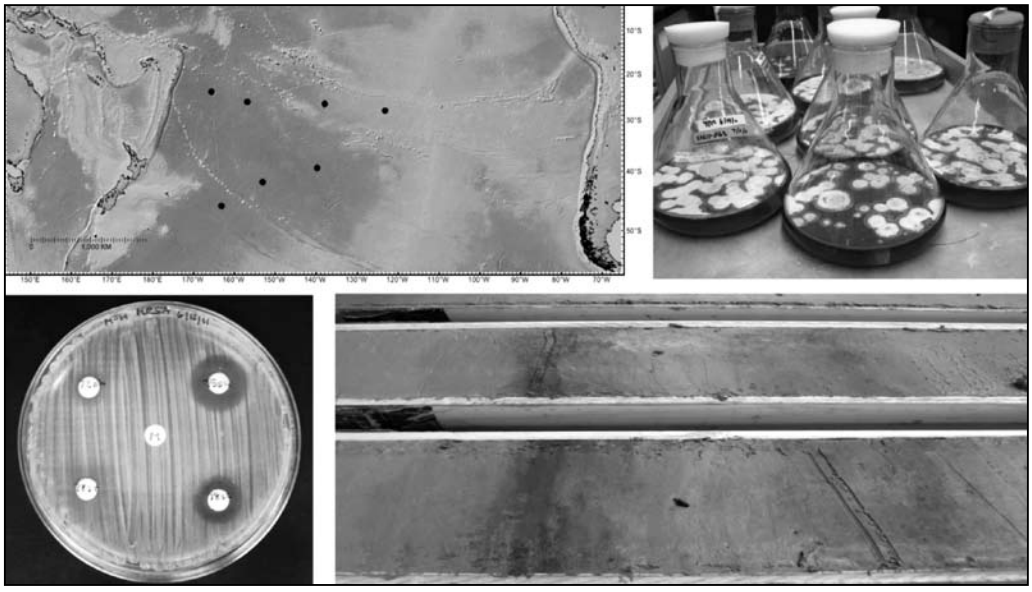

Figure 1. **Discovery of antibiotic compounds from subsurface sediments of the South Pacific Gyre.** Clockwise from top left: Bathymetric map of the South Pacific Gyre with black dots representing sampling sites, large scale static cultivations of a fungal strain isolated from SPG sediments, cross section example of subsurface sediment cores from which the SPG culture collection was isolated, SPG strains were investigated for antibiotic activity using disc diffusion assays.

In 2010, David C. Smith participated in the **Integrated Ocean Drilling Program (DSDP IODP)** Expedition 329 to the **South Pacific Gyre (SPG)**—one of Earth's five major rotating ocean currents—where they cored the sediment stack underlying average ocean depths of 5,057 meters.[7] It possesses the lowest burial rates for organic matter

in the ocean[8] and has been described as the Earth's largest oceanic desert. The sedimentary microbial community has extremely low biomass and metabolic activity and is predicted to be unlike any others of the same depth previously studied by drilling programs.[9] In total, 105 samples were collected from sediment cores within the gyre ranging in depth from 1.3 to 75.3 meters below the seafloor (mbsf) and an additional 27 subcores ranging in depth from 1.4 to 126.9 mbsf were collected from the control site. (Figure 1)

The Rowley group has isolated 150 bacterial and 120 fungal strains from these deep ocean sediments. Taxonomic identification of the bacteria has been undertaken, and many strains identified to date are related to genera and groups recognized to be productive for drug discovery. When grown at atmospheric pressure, room temperature and on standard marine media, a remarkable 60% of bacterial and over 80% of fungal isolates assayed to date from the SPG subsurface sediments produce molecules possessing antibacterial properties against human pathogens, including methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa* PA01, and *Acinetobacter baumannii*.

The next step in this collaborative investigation involves the identification of the exact antibiotics being produced by these microorganisms. Many of the antibiotic producers have been cultured in multi-liter scale, and chemical investigations of their bioactive compounds are underway. Once the antibiotic agents have been purified and the structures have been determined, novel agents will be tested for their growth inhibitory activities against an array of clinically important pathogens at LaPlante's laboratory located at the Providence Veterans Affairs Medical Center.[10, 11]

There are obvious technical challenges to accessing sediments in the deepest regions of the oceans and further difficulties arise in attempting to replicate the extreme environmental conditions of the deep ocean. For example, these microbes are adapted to high pressure, low temperature, and low organic content environments. It is unknown how these parameters may influence the growth of the microorganisms or whether they are critical for the expression of genes leading to antibiotic production. While we can duplicate such conditions in the lab, such cultivations are not conducive to the scale and throughput necessary for drug discovery efforts. Nevertheless, a subset of the deep-sea microbiota can be cultivated under normal laboratory conditions, and these have shown promise for the production of bioactive molecules.

The South Pacific Gyre is just one of five major gyre systems depleted of nutrients year round. The promising antibacterial activities of microbes from the SPG may provide insight into the biomedical potential of similar sedimentary environments underlying other regions of open ocean. Clearly, the deep oceanic subsurface ecosystem should not be overlooked for the discovery of bioactive natural products.

Funding Source

This research is supported by NIH R-15 grant 1R15AI093158-01.

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Disclosure of Financial Interests

Stephanie Forschner-Dancause, PhD, has no financial interests to disclose.

Kerry LaPlante, PharmD, consults for Cubist Pharmaceuticals, Davol, Inc., TheraDoc, and Forrest Laboratories; receives research grant support from Cubist Pharmaceuticals, Inc., Pfizer Pharmaceuticals, Inc., and Theravance, Inc.; and is on the speakers bureau for Cubist Pharmaceuticals, Inc.

David C. Smith, PhD, has no financial interests to disclose.

David C. Rowley, PhD, has no financial interests to disclose.

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